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National Institute of Mental Health

New Directions in Clinical Neuroscience

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Director, NIMH/NIH

Acting Director, NCATS/NIH

Disclosures: None

Federal employee: Public filing of all financial interests

Impact of Research on Heart Disease

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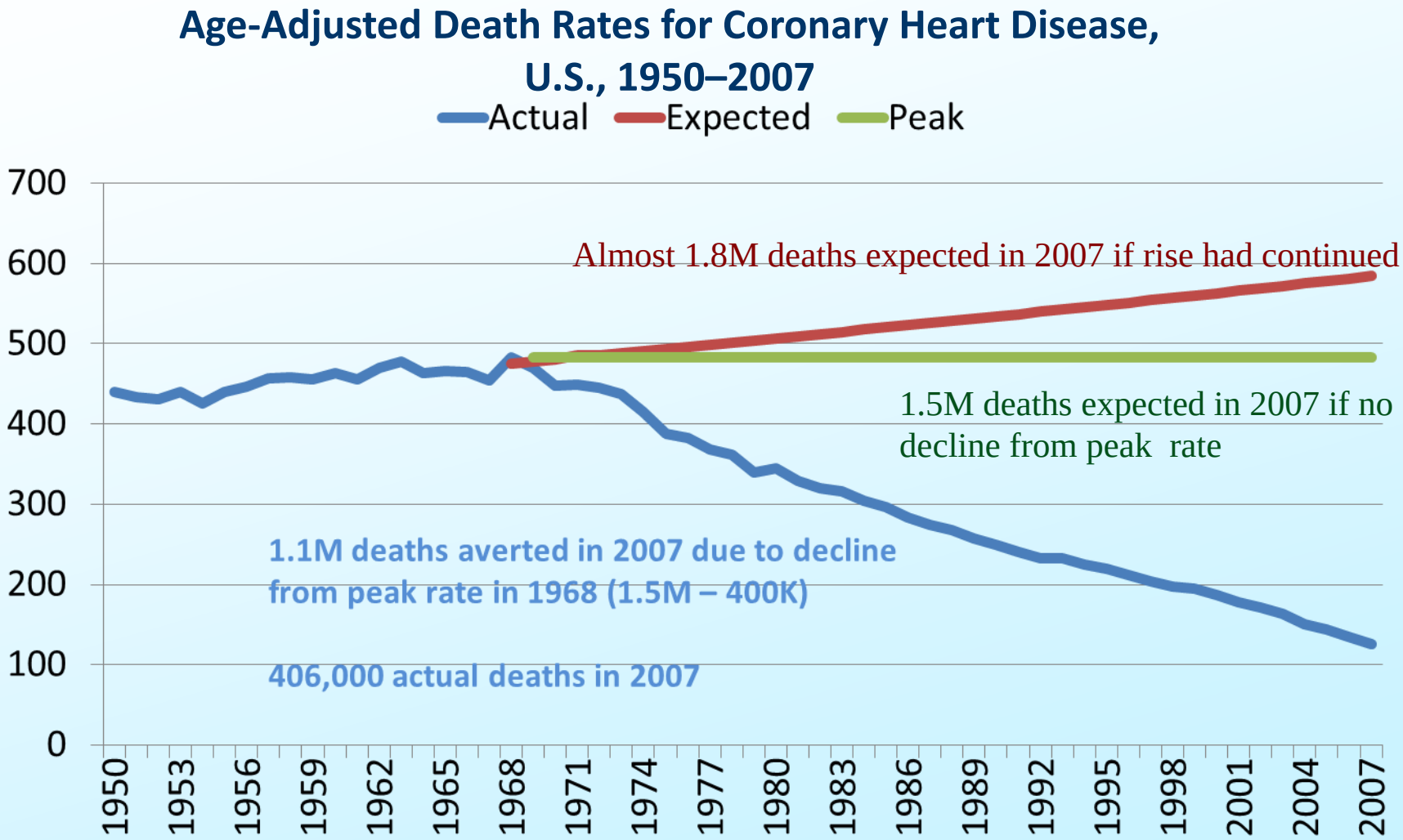

Source: NHLBI Factbook, 2010

Success Stories in Clinical Neuroscience

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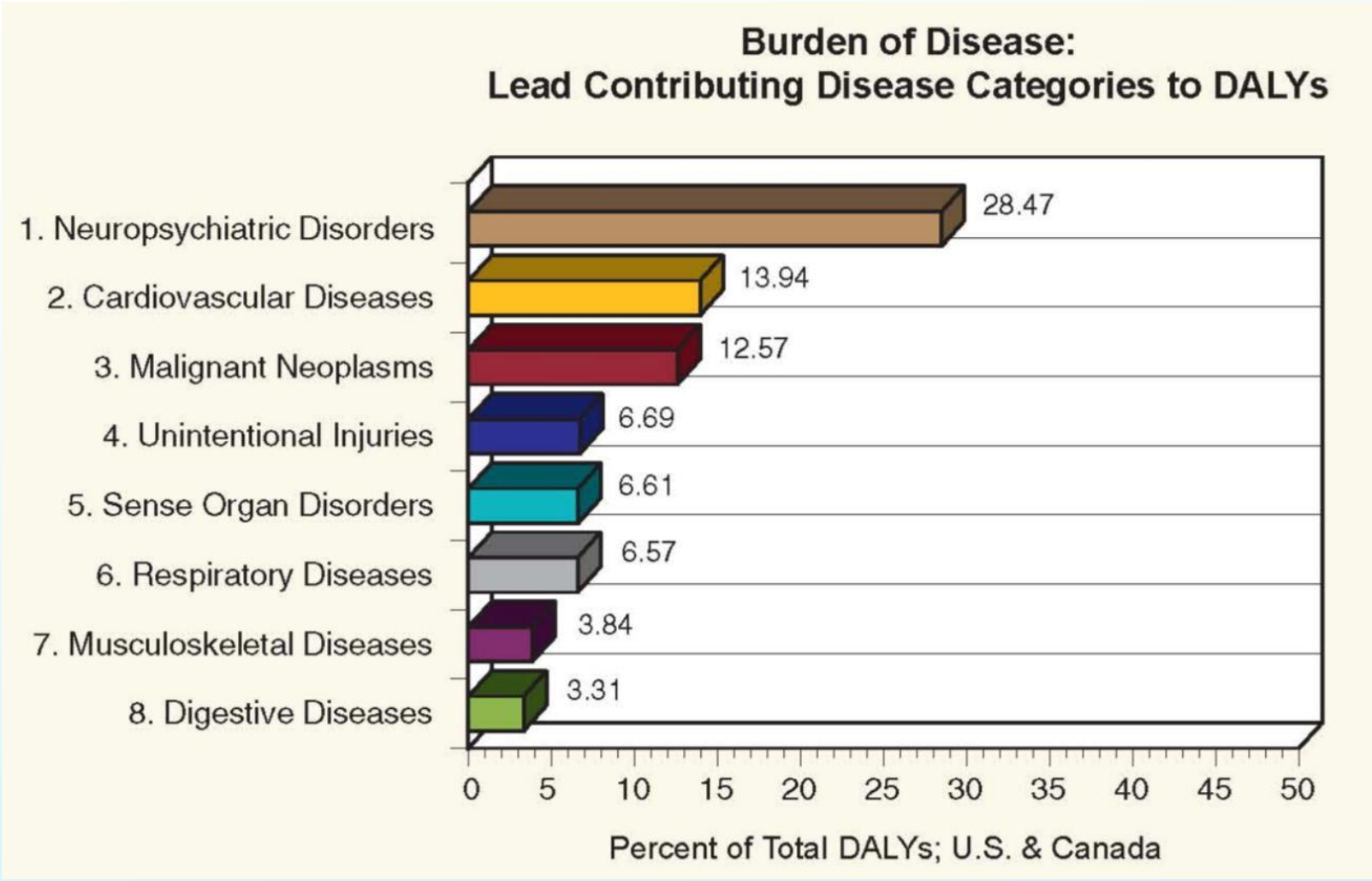
- Acute ischemic stroke – tPA within 3 hours of onset, 30% full recovery
- MS – treatments that slow progression and biomarker to track outcome
- Early Parkinson's excellent response to DA agonists
- Mood, anxiety, and psychotic disorders – excellent response to meds and psychosocial Rx in subset
- DBS effects in Parkinson's, tremor, refractory depression

But, there is still much to do….

- Diagnosis is by observation, detection is late, prediction is poor
- Etiology is unknown for many disorders; prevention is not well-developed for most disorders
- Treatment is trial and error – no cures, no vaccines.

Bottom line:
Revolution in neuroscience, but…
this revolution remains to be translated to better diagnostics, preventions, and cures

Brain Disorders are Chronic and Disabling



Source: WHO 2008

Brain Disorders are Deadly

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- Over 36,000 suicides per year in the U.S. (2009; CDC)
  - 90% related to mental illness (Mann, 2002)
  - More suicides than combat deaths in US Army (DoD, 2011)
  - 3rd leading source of mortality ages 15 - 24
- For context:
  - 17,000 homicides (2010)
  - 34,000 traffic fatalities (2010; NTSB)
  - < 20, 000 AIDS deaths (2009, CDC)

Life expectancy reduced 8 years with serious mental illness (cardiopulmonary, metabolic, multiple conditions)
(Druss et al., Medical Care, 2011)

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The Most Costly Conditions

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Economic Burden of Noncommunicable Diseases, 2011-2030

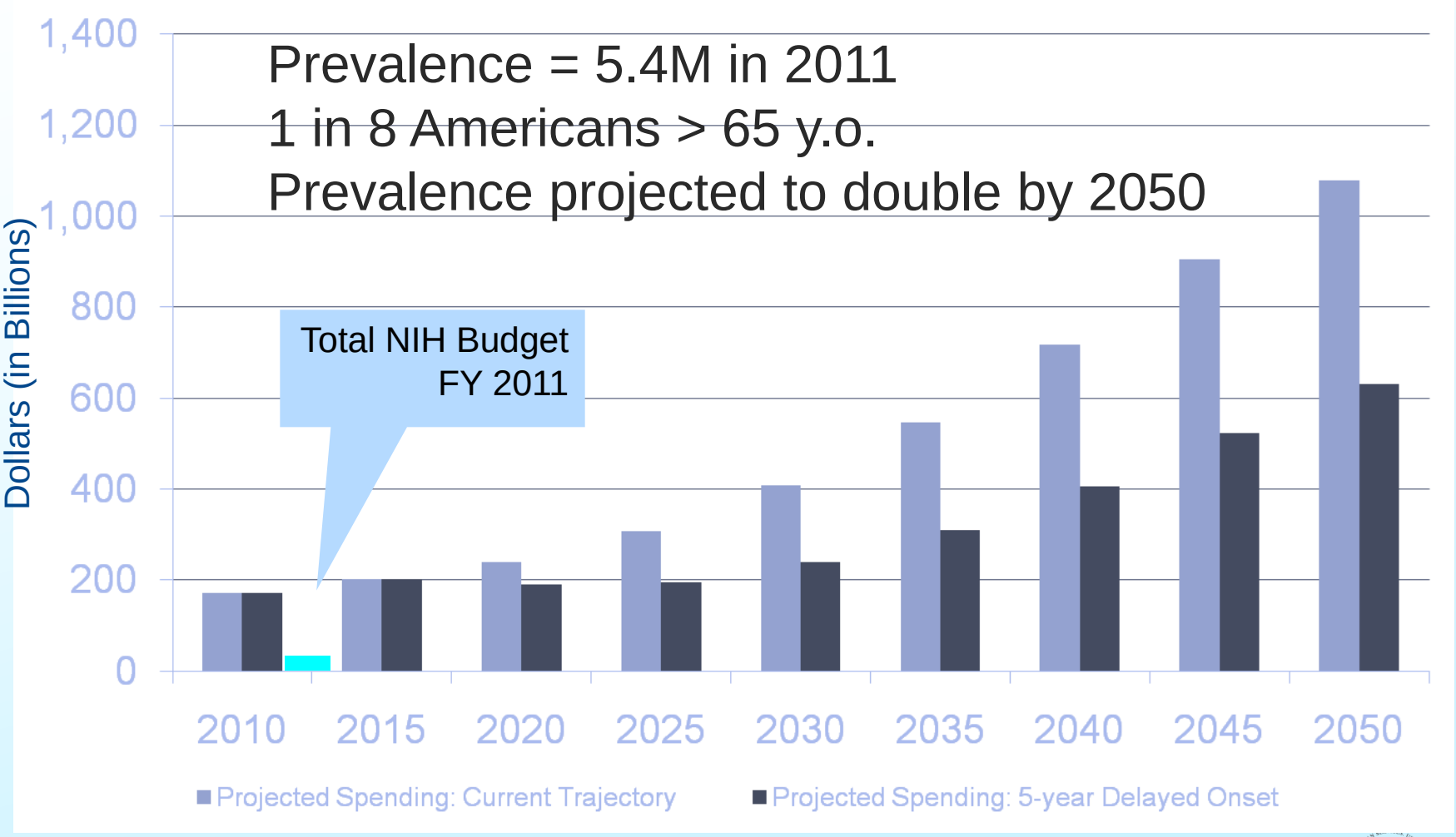
(trillions of US$ 2010)

Country income group	Diabetes	Cardiovascular diseases	Chronic Respiratory diseases	Cancer	Mental Illness	Total
High	0.9	8.5	1.6	5.4	9.0	25.5
Upper-middle	0.6	4.8	2.2	2.3	5.1	14.9
Lower-middle	0.2	2.0	0.9	0.5	1.9	5.5
Low	0.0	0.3	0.1	0.1	0.3	0.9
LMIC	0.8	7.1	3.2	2.9	7.3	21.3
World	1.7	15.6	4.8	8.3	16.3	46.7

Source: The Global Economic Burden of Noncommunicable Diseases. WEF, 2011

US Annual Costs > $300B for SMI (Insel, AJP, 2008)

Burden of Alzheimer's Disease Over Time: Projected Spending



Source: Alzheimer's Association, *Changing the Trajectory of Alzheimer's Disease: A National Imperative* (2010).

Multi-level Scientific Approach: Our Toolbox

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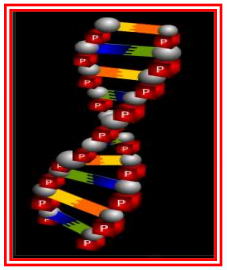



Molecules	Cells	Systems	Individual	Social
GWAS	Stem Cells	Electrode	Sensors	Web 2.0
Sequencing	RNAseq	Arrays	Eye gaze	Knowledge
Transgenics	Proteomics	Zebrafish	Cognitive	Management
Knock-outs	Optical	Imaging	Tools	Crowd Sourcing
Epigenetics	imaging	ChR-2	Epidemiology	
Databases	Databases	Databases	Databases	Databases

Genetics: Transforming Technologies
Sequencing Costs Drop Faster than Moore's Law

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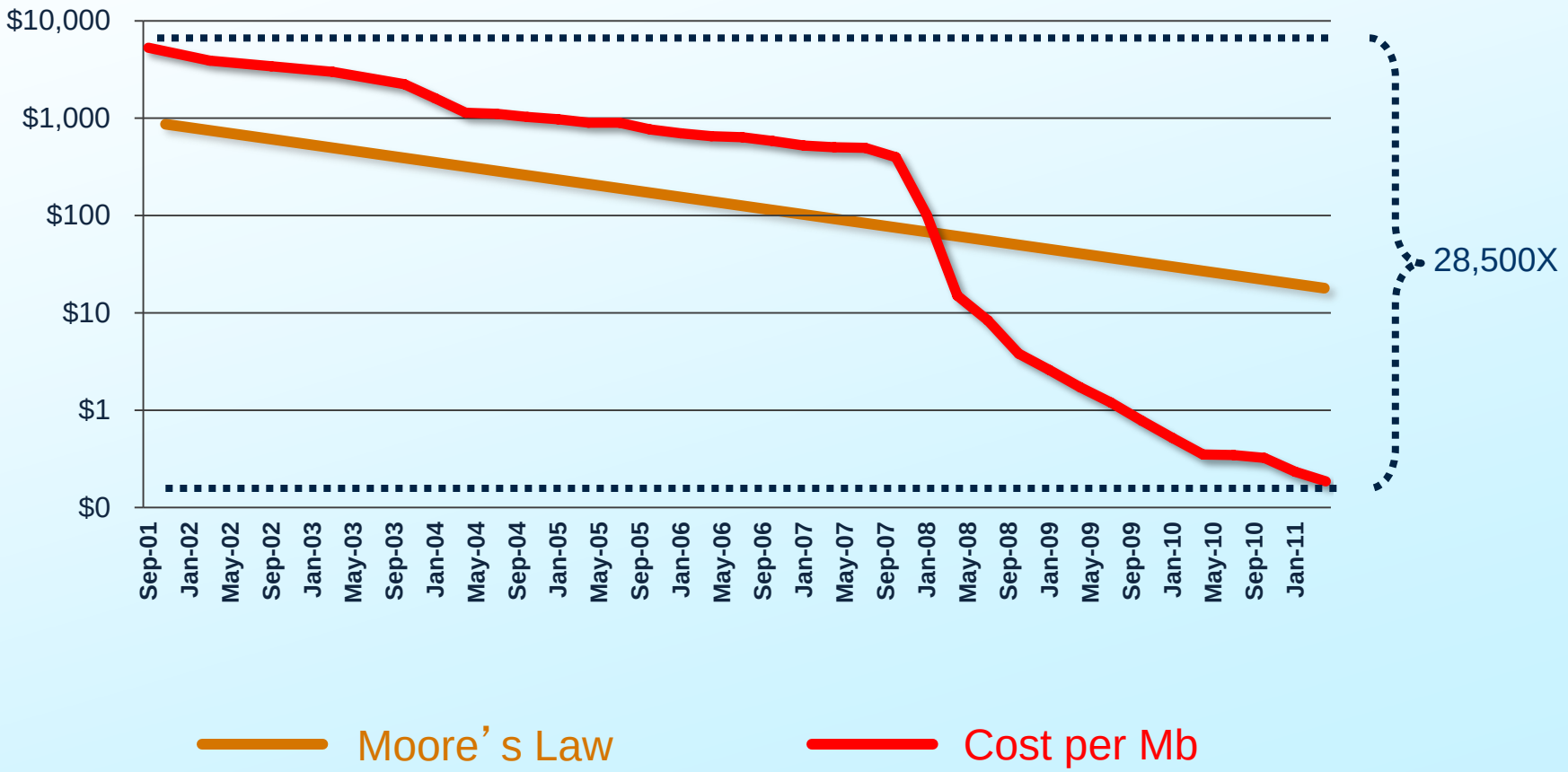
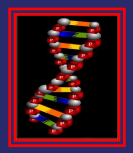
Cost per Megabase of DNA Sequence





Genetics – What Have We Learned?

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- Genetic ≠ Inherited (spontaneous mutations are common)
- Genetic ≠ Causal (genes confer risk and resilience)
- Genetics may reveal pathways involved in risk and resilience
- Genetics provides a mechanism for experience to influence brain and behavior (epigenomics!)
- Genetics (genomics) is our most powerful tool for understanding individual variation (and that variation is huge!)

Transformative Technologies – iPS cells

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Science

AAAS

Science **318**, 1917 (2007)

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Junying Yu,[1,2]* Maxim A. Vodyanik,[2] Kim Smuga-Otto,[1,2] Jessica Antosiewicz-Bourget,[1,2] Jennifer L. Frane,[1] Shulan Tian,[3] Jeff Nie,[3] Gudrun A. Jonsdottir,[3] Victor Ruotti,[3] Ron Stewart,[3] Igor I. Slukvin,[2,4] James A. Thomson[1,2,5]*

Cell *131*, 861–872, November 30, 2007 ©2007 Elsevier Inc.

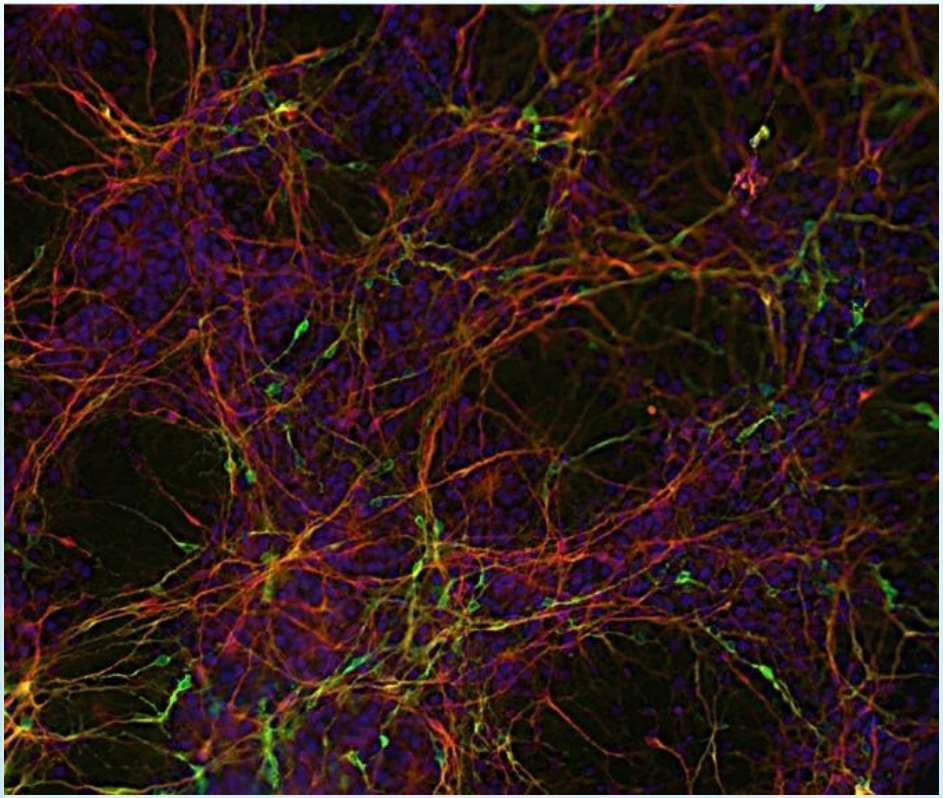
Cell

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
[3]Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
[4]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

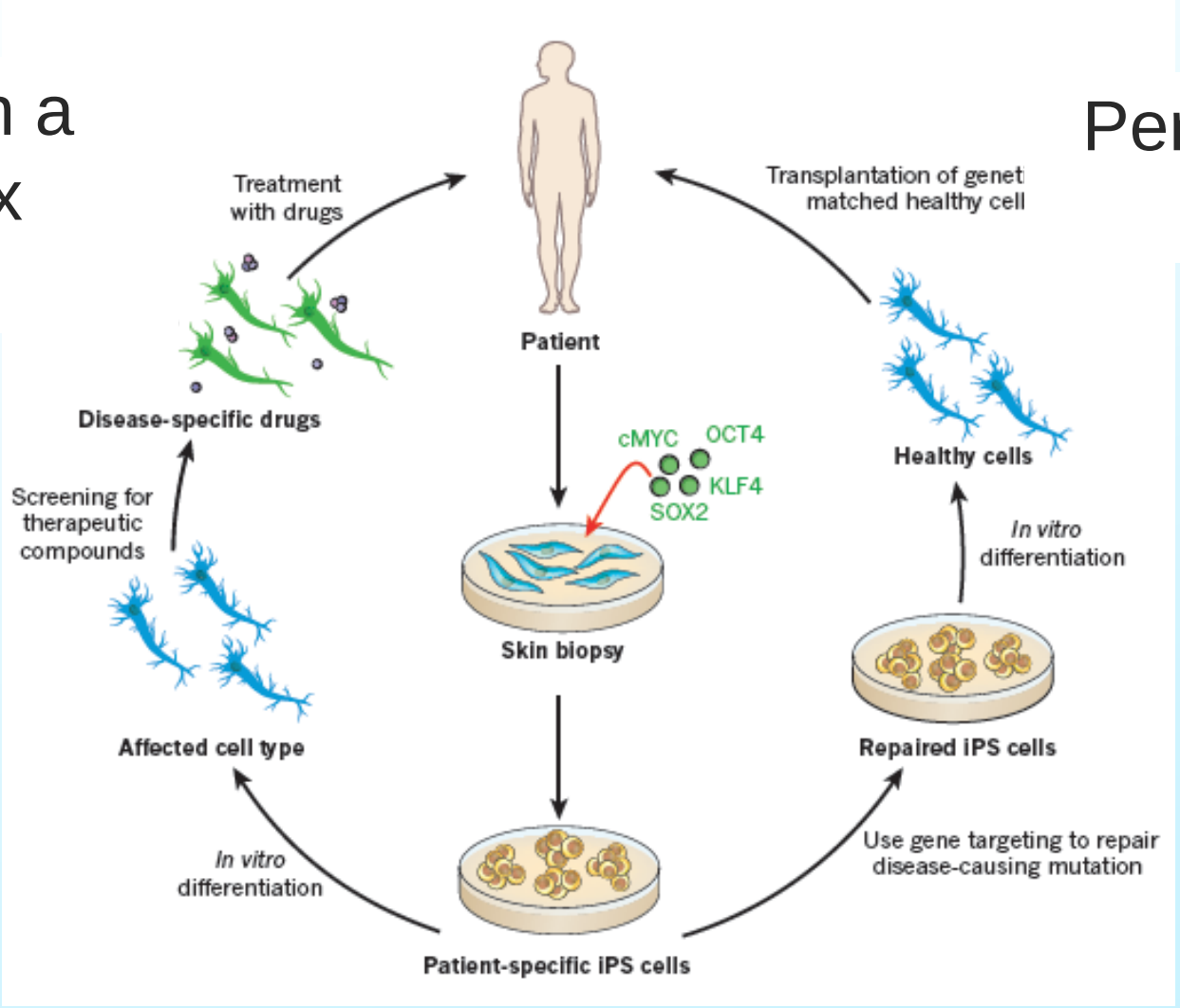
Map2, **TH**, **DAPI**



Dolmetsch lab, 2012

Transformative Technologies – iPS cells

Disease in a dish for Rx screening



Personalized cell Rx

Nature, Jan 19, 2012 vol 481

Cell Biology: dendrite dynamics in Timothy syndrome derived neurons

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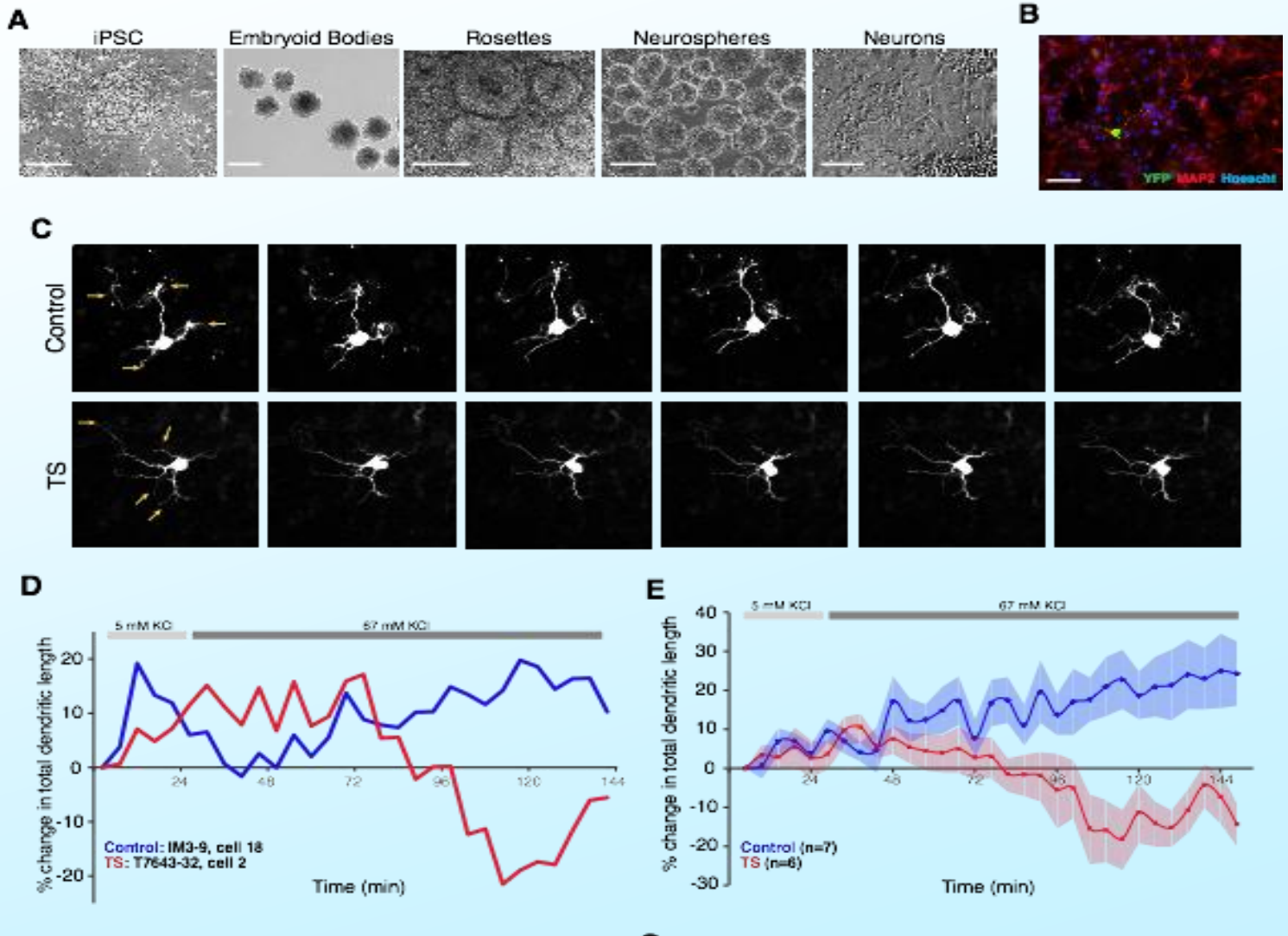
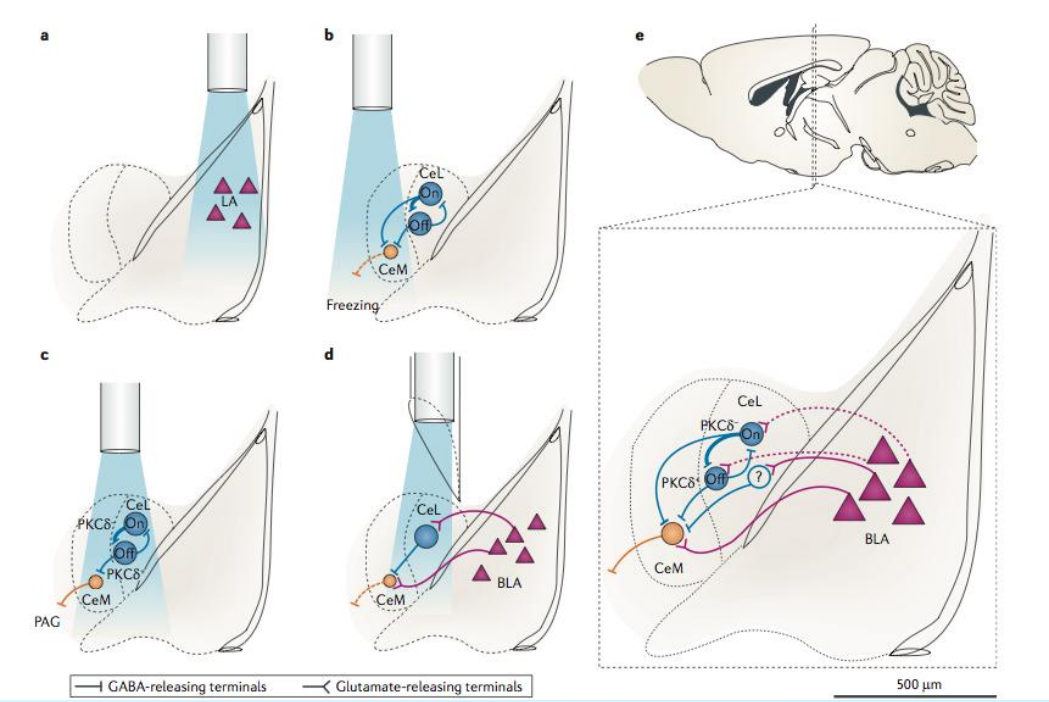
Source: Pasca and Dolmetsch



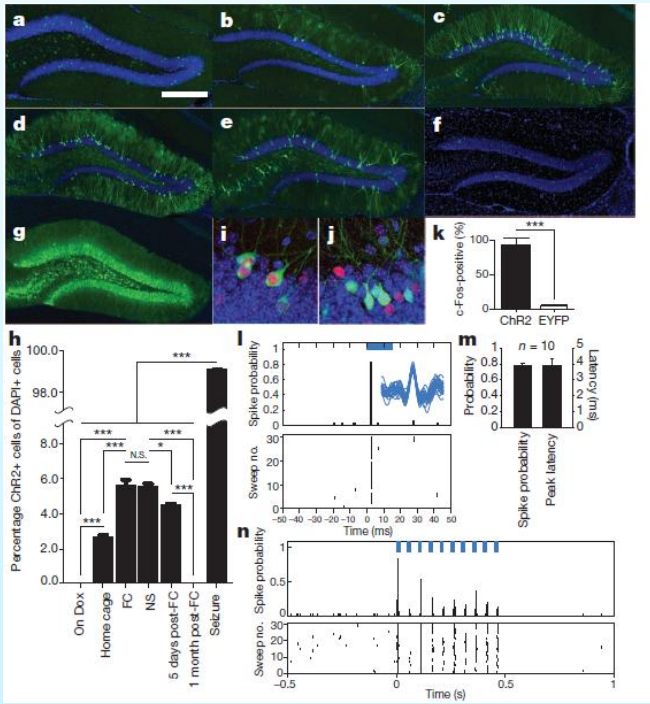
Optogenetics

Functional dissection of amygdala microcircuitry using optogenetic tools



Tye and Disseroth, Nat Neurosci Rev 2012

Optogenetic reactivation of hippocampal neurons after fear conditioning. Light-induced fear memory recall.



Liu et al., Nature 2012

Systems: Transforming Technology

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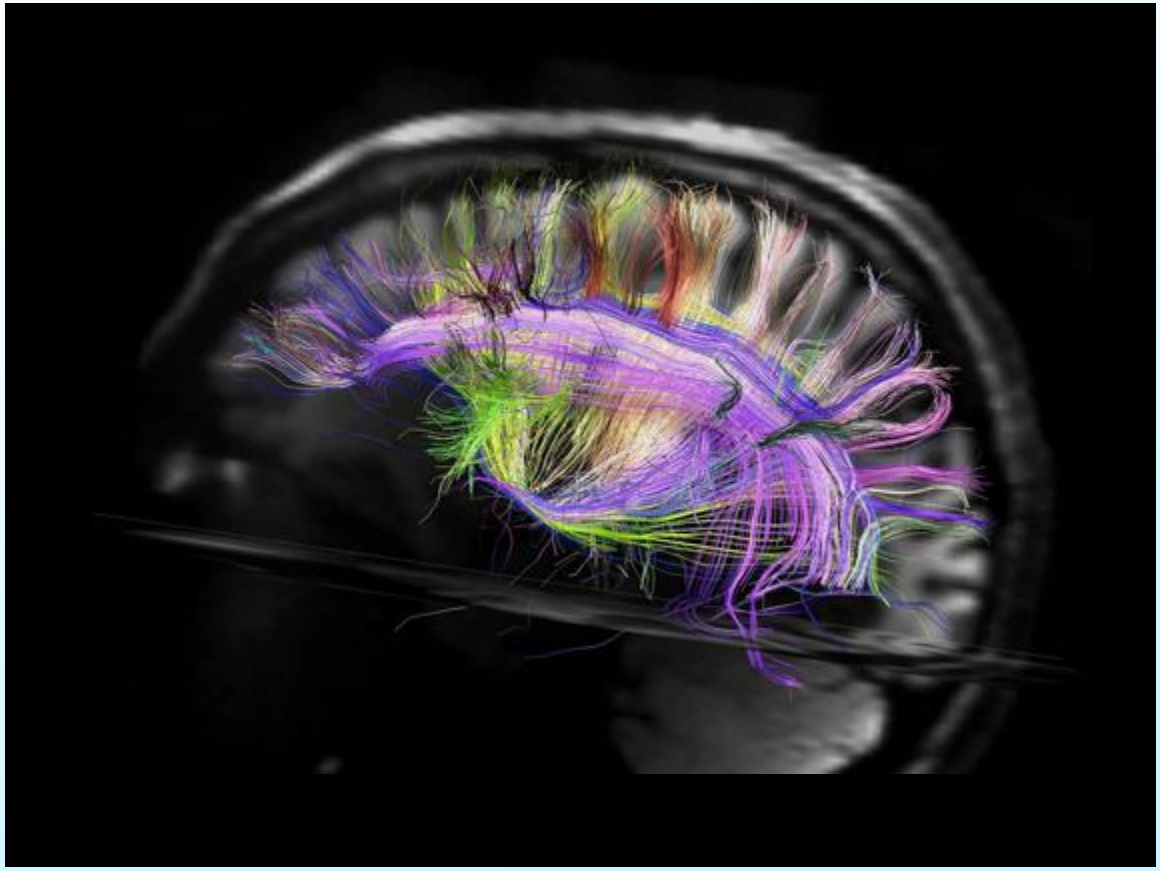
Mapping the Connectome: From DTI to DSI



Wedeen V.J, Science, 2012

Individual: Transforming Technologies

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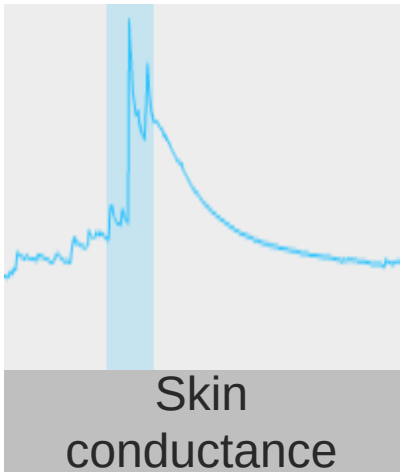
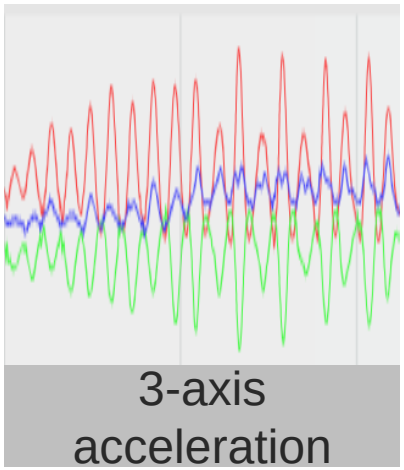
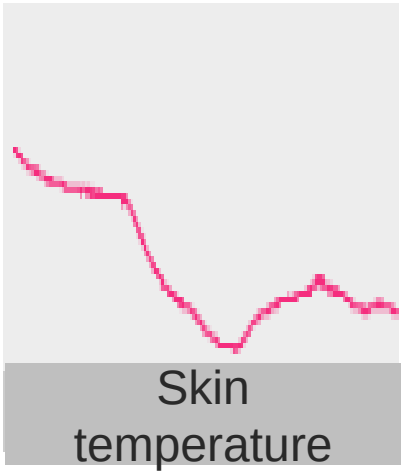
Objective Measures



Skin conductance



3-axis acceleration



Skin temperature

Activity, Sleep, EDA, EKG, EEG, Stereotypies, Temp.

Non-invasive 24/7 inexpensive phenotyping

MIT MEDIA LAB

Roz Picard and colleagues

Social: Transforming Technologies
Crowd Sourcing

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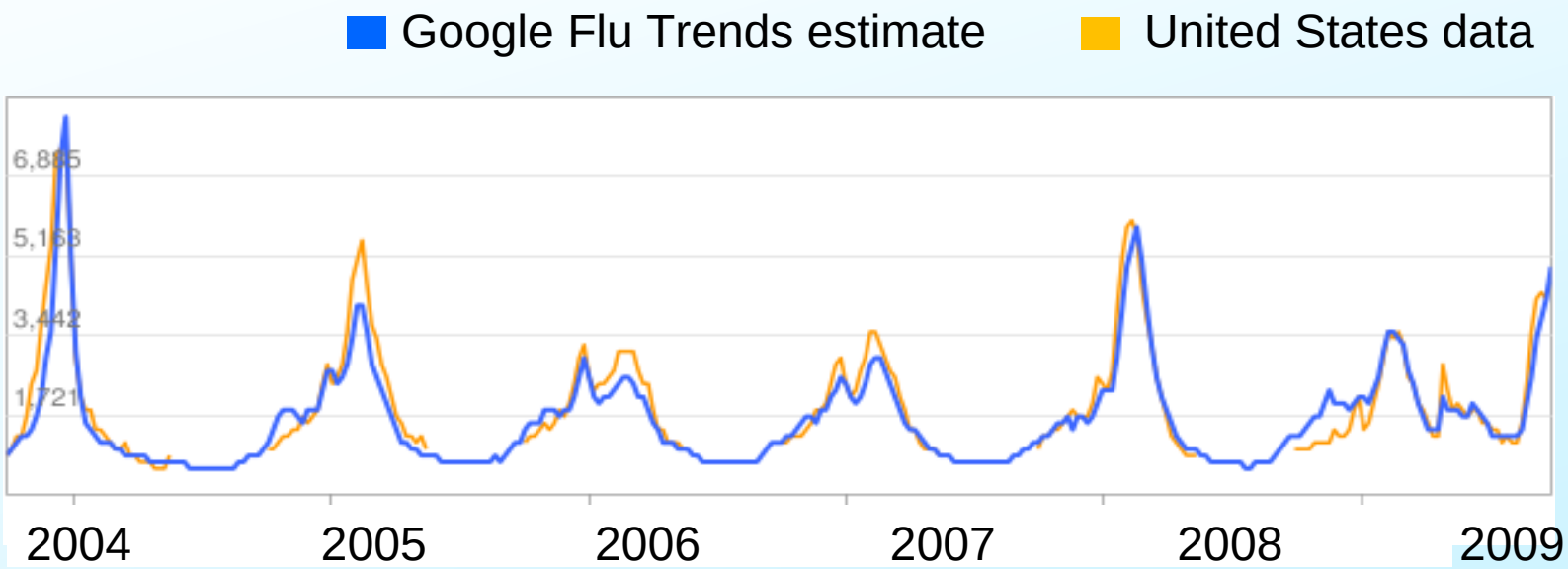
United States Flu Estimate



United States: Influenza-like illness (ILI) data provided by the U.S. Centers for Disease Control

From the Google Flu Trends web site: www.google.org/flutrends/

Social: Transforming Technologies

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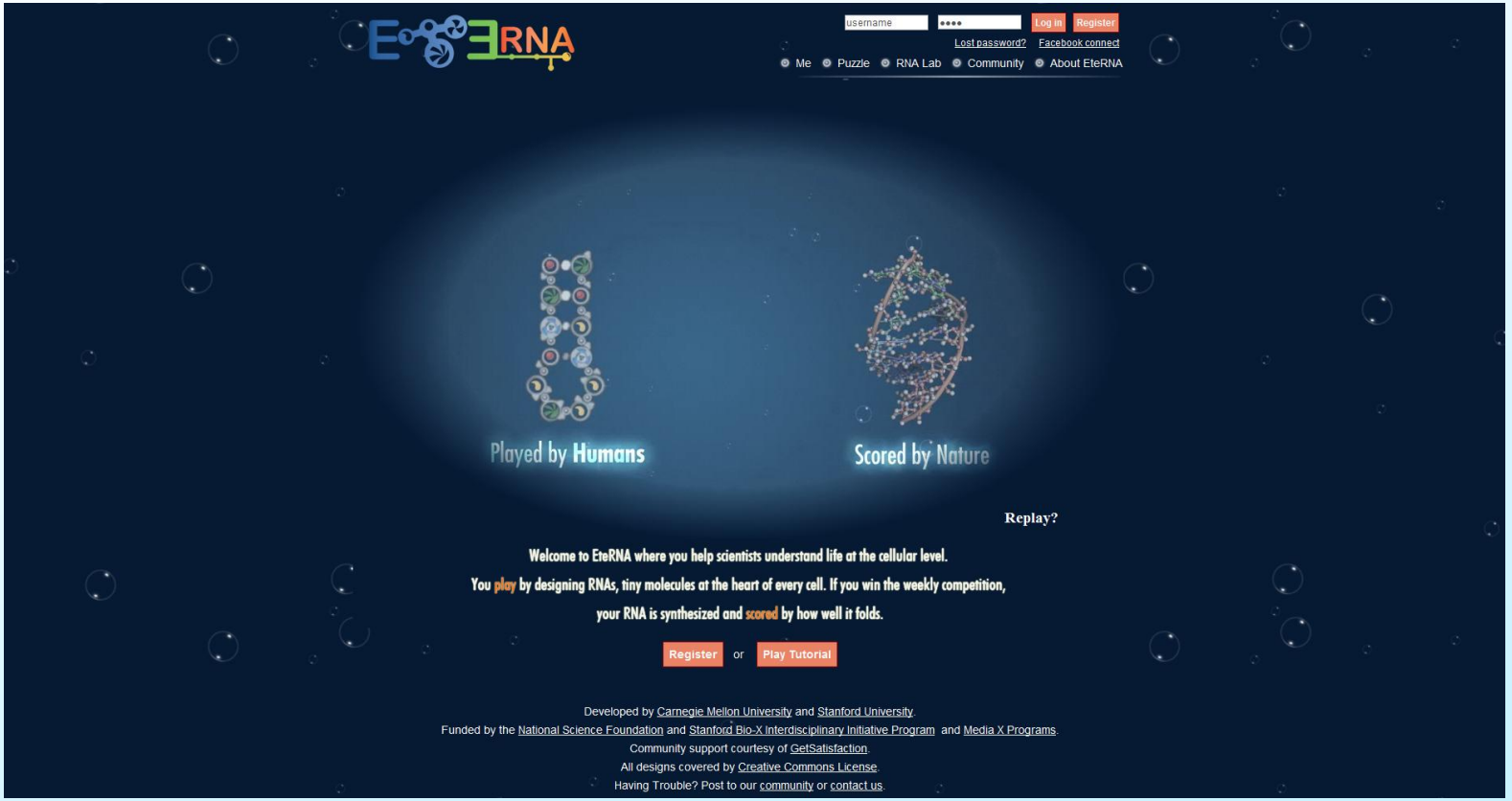
Crowd sourcing science: RNA nanostructure as a Rubik's Cube 6,000 players worldwide; Social networks forming to compete



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Multi-level Scientific Approach: Our Toolbox

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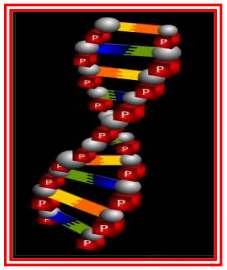



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Epigenetics	imaging	ChR-2	Epidemiology	
Databases	Databases	Databases	Databases	Databases

Where are we stuck?

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- We don’t understand the biology of normal or abnormal brain development, function, and aging
- We arrive too late to preempt the major symptoms
- We are looking for home runs instead of base hits (and grand slams)

Drug development is slow and risky

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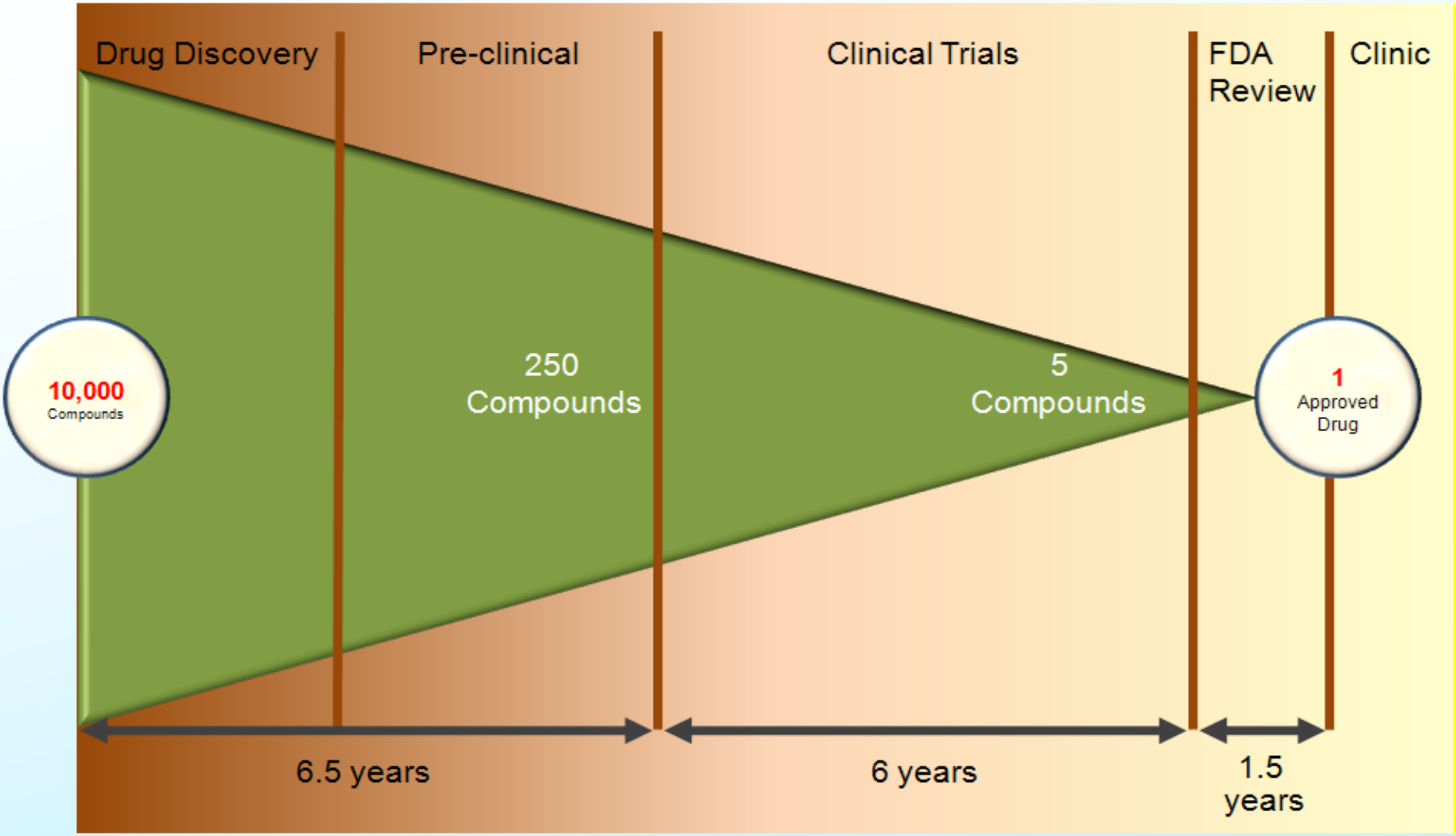

Trends in Drug Development: Eroom's Law

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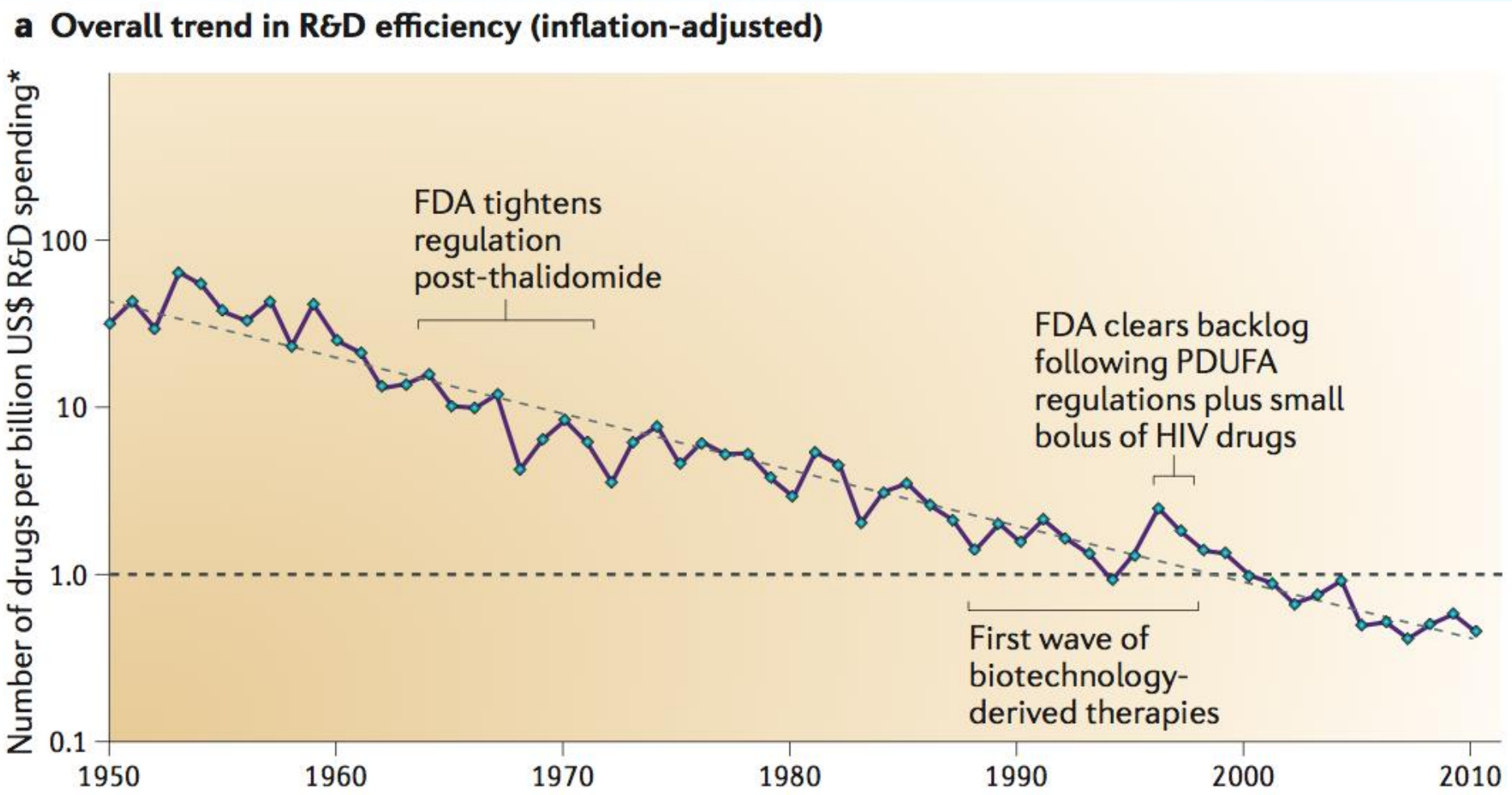

Scannell et al, NRDD, 2012

Advancing Translational Science: Experimental Medicine

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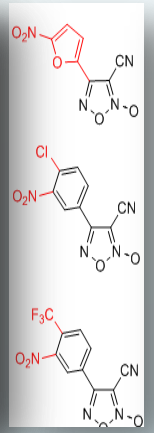
Trials to confirm or exclude “targets”; drugs as tools for fast fail



Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

New Paradigm: Experimental Medicine

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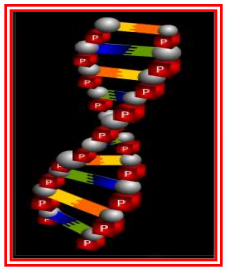
- Move quickly into humans
- Focus on Phase 0 – Phase 2a
- Fail quickly and often
- Target engagement (imaging, MOA)
- Precompetitive partnerships (biomarkers)
- Share data (especially failures)

New Targets?



Protective LOF mutations, Pathway targets, epigenetics

Cell replacement Rx, Plasticity agents

Circuit based Rx, rTMS, DBS

Cognitive training

Peer support

Combined Therapies

Epigenetics – A Possible Target?

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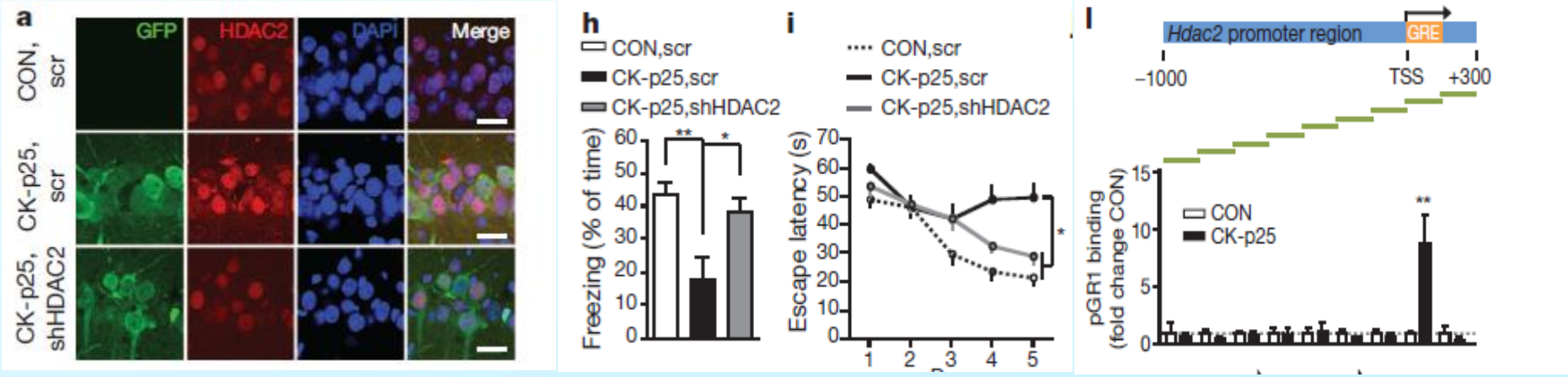
LETTER

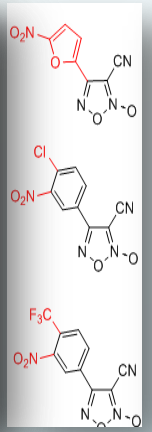
doi:10.1038/nature10849

An epigenetic blockade of cognitive functions in the neurodegenerating brain

Johannes Gräff[1,2,3], Damien Rei[1,2], Ji-Song Guan[1,2,3], Wen-Yuan Wang[1,2,3], Jinsoo Seo[1,2], Krista M. Hennig[3,4], Thomas J. F. Nieland[3], Daniel M. Fass[3,4], Patricia F. Kao[5], Martin Kahn[1], Susan C. Su[1,2], Alireza Samiei[1], Nadine Joseph[1,2,3], Stephen J. Haggarty[3,4], Ivana Delalle[5] & Li-Huei Tsai[1,2,3]



Advancing Translational Science: Repurposing



Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

NCATS Comprehensive Drug Repurposing Program

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The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

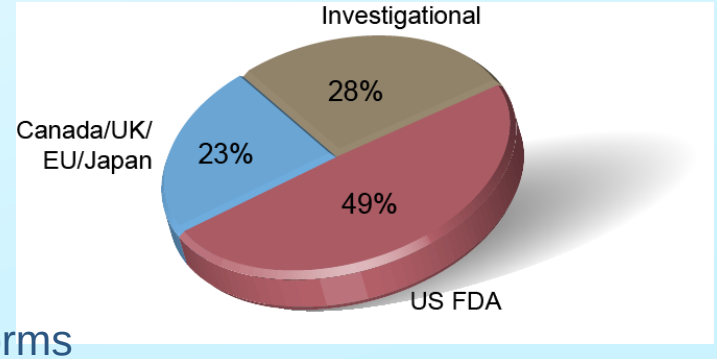
Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

www.ScienceTranslationalMedicine.org 27 April 2011 Vol 3 Issue 80 80ps16

NCATS Pharmaceutical Collection Status April 2011

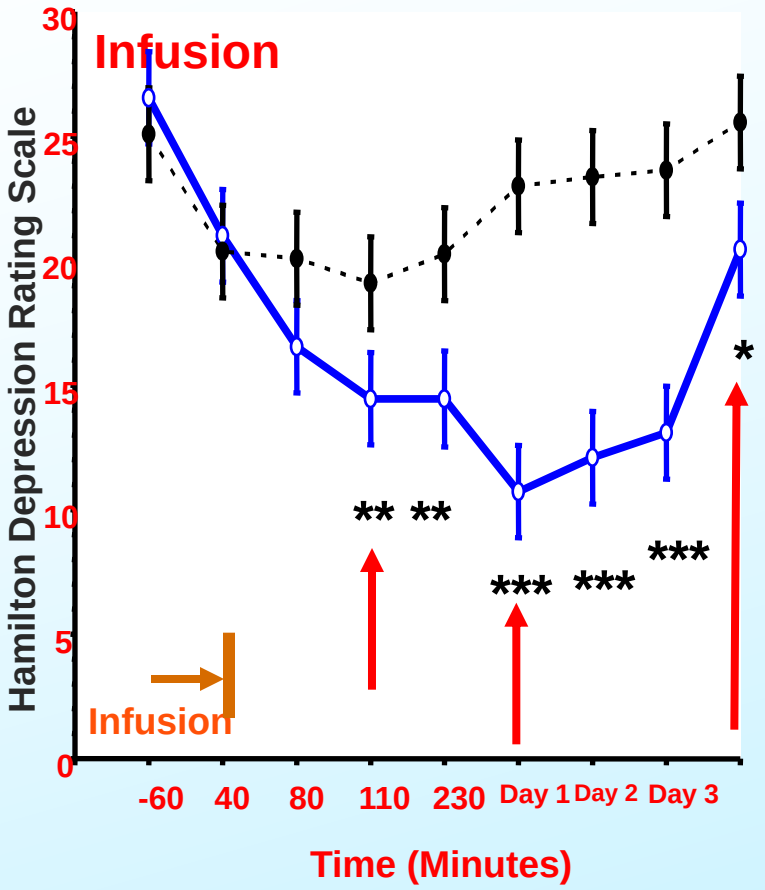
Drug Source	In house	Procurement in process
US FDA	1635	182
UK/EU/Canada/Japan	756	177
Investigational	928	3953
Total Approved	2391	359
Total	**3319**	**4312**

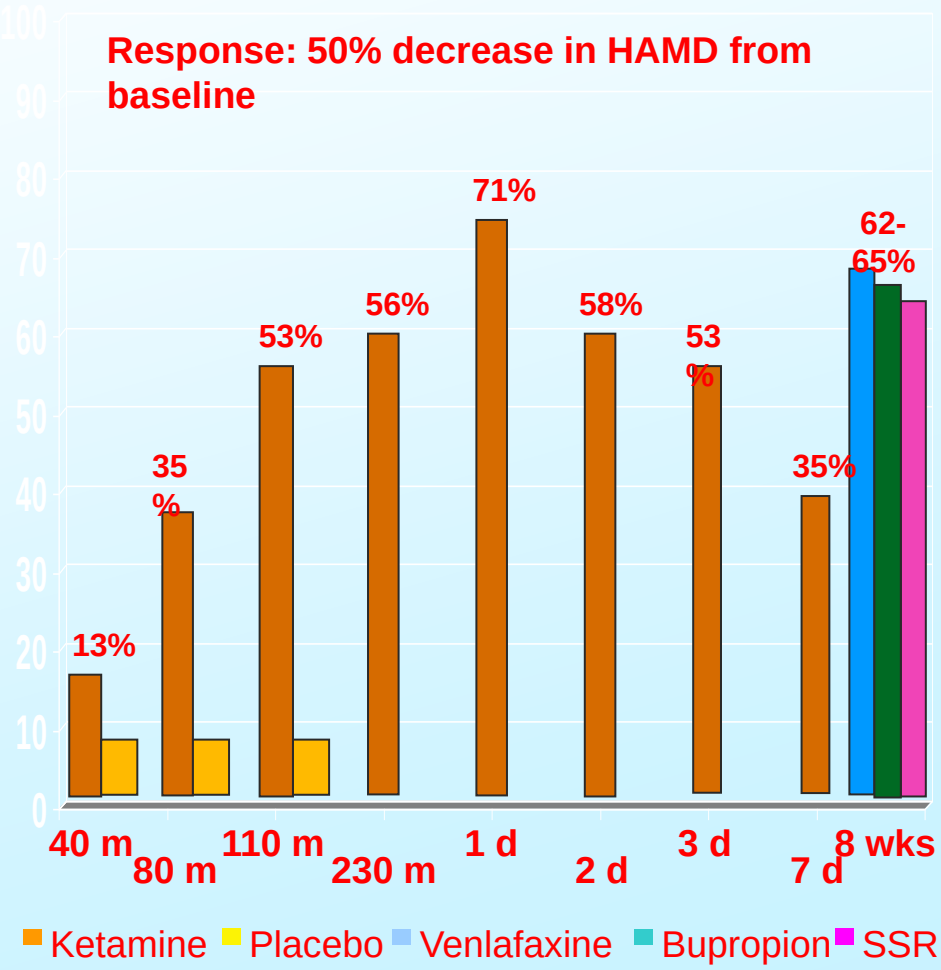
- Informatics sources for NPC
  - US FDA: Orange Book, OTC, NDC, Green Book, Drugs at FDA
  - Britain NHS
  - EMEA
  - Health Canada
  - Japan NHI
- Physical sources for NPC
  - Procurement from >70 suppliers worldwide
  - In-house purification of APIs from marketed forms
  - Synthesis



Drug plate composition

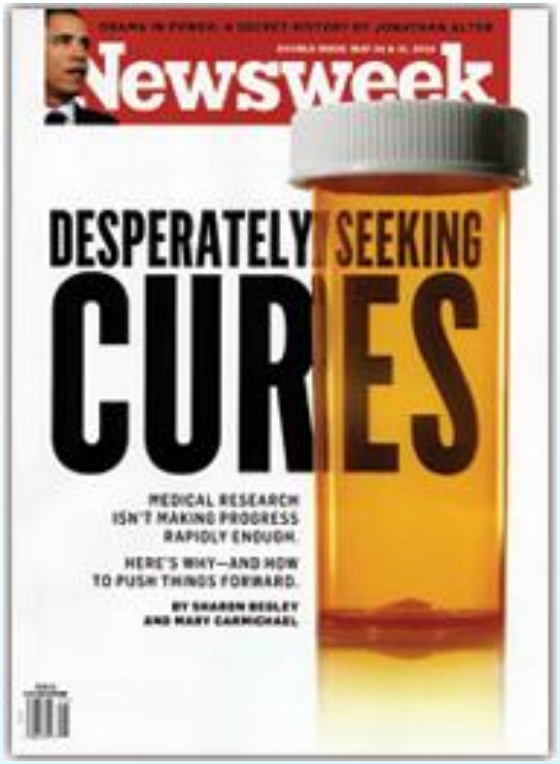
Rx depression in 3 hours instead of 8 weeks





Zarate et al. Arch Gen Psychiatry, 2006

Neuroscience: Lost in Translation?



NIH & FDA

Industry

Academia

Patients

ADNI

FNIH (Biomarkers Consortium)

NCATS (New Uses for Existing Drugs)

Precompetitive Partnerships

New Opportunities for Therapeutics

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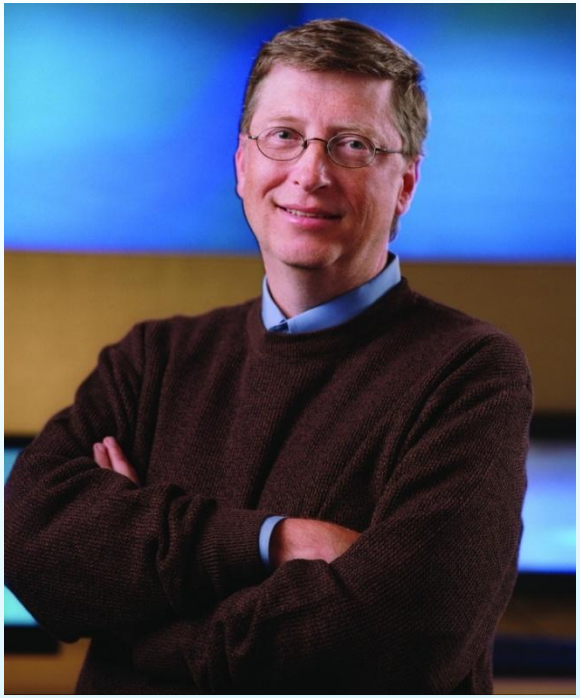
Revolutionary neuroscience:

Epigenetics
New molecular targets
Rapid treatments
Circuit-based Rx
Cognitive training
Devices
Combined interventions

Transforming Translation:

Precompetitive partnerships
Experimental medicine
Precision medicine
Regulatory science
Patient centered care

Finally



"We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten."

--Bill Gates Jr.